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Alexandra Verónica Salgado Leite Rodrigues

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Alexandra Verónica Salgado Leite Rodrigues

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NOME

Alexandra Verónica Salgado Leite Rodrigues

NÚMERO DE ESTUDANTE

201200177

E-MAIL

alexandrasrodrigues@gmail.com

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ORIENTADOR

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Assinatura conforme cartão de identificação: Alexandra Verónica Salgado Leite Rodrigues

Review Article

Corresponding Authors:

Alexandra VSL Rodrigues

Address: Department of Biomedicine-Pharmacology and Therapeutics Unit

FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, PORTUGAL

e-mail: alexandraslrodrigues@gmail.com

Dimethyltryptamine: endogenous role and therapeutic potential

Alexandra VSL Rodrigues [1], Maria A Viera-Coelho [1,2]

Faculdade de Medicina da Universidade do Porto, Portugal

[1] Department of Biomedicine-Pharmacology and Therapeutics unit, Faculty of Medicine, University of Porto, Porto, Portugal.

[2] Psychiatry and Mental Health Clinic, Hospital de São João, Porto, Portugal.

Abstract

N, N-dimethyltryptamine (DMT) is an indole alkaloid produced by a number of plants and animals, including humans. Its psychoactive effects were first described in 1956 by Stephen Szára, but have been exploited for centuries by South American indigenous populations throught the use of ayahuasca, an infusion made with a mixture of plants rich in the psychadelic DMT. In the present review, we assess the state of the art regarding a putative role for endogenous DMT and potential future clinical applications. We gathered papers published until 20 March 2018 and included in the PubMed database using the words: N,N-dimethyltryptamine and ayahuasca. While the role of endogenous DMT remains unclear, ayahuasca has promising results in anxiety, depression and substance dependence. Thus, we conclude that although little has been proven, much has been speculated about the endogenous role of DMT. Overcoming the methodological setbacks is crucial to develop research further. In the other hand, ayahuasca has a good safety profile and growing evidence it could be used in therapy for some neuropsychiatric diseases.

Keywords

N,N-dimethyltryptamine, 5-HT receptors, Ayahuasca, Anxiety, Depression, Substance Dependence

Introduction

N,N-dimethyltryptamine (DMT) is an indole alkaloid widely found in nature. It is an endogenous compound in animals and in a extensive variety of plants around the globe[1]. DMT can be produced in the human body, in very small quantities [2] and is also produced by rats [3]. This presence across species may suggest that it has an important biological role conserved throughout the evolution, or that it is a remnant of a biological function that has fallen into disuse. When administered exogenously, due to its hallucinogenic properties, DMT has been used to study "outside the body" experiences and dreams, while also being used as a model for psychosis [4,5].

The exogenous administration of DMT is mostly associated with ayahuasca, which is a psychotropic plant tea traditionally used for centuries by indigenous and shamanists of Amazonian countries such as Brazil, Colombia, Peru, and Ecuador for magical- religious and therapeutic purposes. However, in the last 25 years, ritual and therapeutic use of Ayahuasca has spread from small cities in the Amazonian jungle to the urban centers across the world [6].

Ayahuasca is usually obtained by boiling the leaves of the bush Psychotria viridis (known as chacrona or queen), rich in DMT, and stalks of the vine Banisteriopsis caapi which contains β-carboline alkaloids such as harmine, tetrahydroharmine and harmaline, that are reversible inhibitors of monoamine oxidase A (MAO-A). DMT is a substrate for MAO-A, so it is rapidly metabolized, failing to produce the known effects if administered without an inhibitor of this enzyme[1].

While research on pure DMT has focused on the basic physiological effects and psychotomimesis of DMT which is essential for understanding its endogenous role, the rapid growth of ayahuasca as a cultural phenomenon and religious sacrament has ignited curiosity about its exogenous effects. Indeed, as the research on dissociative drugs such as psilocybin has been of increasing importance in the affective spectrum pathology[7] the therapeutic potential of ayahuasca has been rising and bringing promising results[8].

The present literature review aims to situate the research on the endogenous role of DMT, as well as to point out the therapeutic potential based on the research with ayahuasca.

N,N-dimethyltryptamine

Pharmacology

- *Pharmacokinetics*

A review by Barker in 2012 evaluated 69 studies reporting the detection of claimed endogenous hallucinogens DMT; 5-hydroxy-DMT (HDMT, bufotenine); 5-methoxy-DMT (MDMT) in humans and concluded that exists evidence support for the confirmation of their presence in certain human biological fluids [cerebrospinal fluid (CSF; DMT and MDMT), blood (DMT and HDMT) and urine (DMT and HDMT)]. To assess the possible origin of these substances, the same group used liquid chromatography-tandem mass spectrometry (LC/MS/MS) to analyze micro-dialysates from the rat pineal gland, showing the presence of DMT[2,3]. DMT may be produced in different tissues, but due to the methodological inability to directly detect it and to its small endogenous production, more studies need to be performed.

Given these issues, exogenous DMT was used in studies to clarify its kinetics. DMT is synthesized by decarboxylation to tryptamine of the essential amino acid tryptophan. Tryptamine is then transmethylated by the indolethylamine-N-methyltransferase (INMT) enzyme (using S-adenosyl methionine as a substrate), which catalyzes the addition of methyl groups resulting in the production of N-methyltryptamine (NMT) and DMT. NMT can also act as a substrate for INMT-dependent DMT biosynthesis. INMT is widely expressed in the body, primarily in peripheral tissue such as the lungs, thyroid and adrenal gland. INMT is located in intermediate levels in placenta, skeletal muscle, heart, small intestine, stomach, retina, pancreas, and lymph nodes. It is densely located in the anterior horn of the spinal cord. Within the human brain, the highest INMT activity has been found in the uncus, medulla, amygdala, frontal cortex, and in the fronto-parietal and temporal lobes. Further, Cozzi et al. (2011)[1] demonstrated INMT expression in the pineal gland as well[2]. Nonetheless, given that there are other substrates for INNT, its expression does not reflect presence of DMT[9].

DMT is not active when oral administrated, probably due to its rapid degradation by MAO enzyme which catalyzes the oxidation of biogenic amines. Ayahuasca contains the carboline alkaloids harmine, harmaline and tetrahydro-harmine, that are potent MAO inhibitors, preventing the first-pass oxidative deamination of DMT. DMT can act as monoamine oxidase inhibitor at high doses (maximum effects at 50 mg/kg), and is selective for MAO-A. In the rat brain, proniazid (MAO-A inhibitor) extends the half-life of DMT[1].

None of the metabolites produced DMT-like effects in both human and rodent models. From the MAO pathway are produced several molecules: NMT, 6-hydroxy-DMT (6-OH-DMT), 6-OH-DMT-N-oxide (6-OH-DMT-NO), DMT-N-oxide (DMT-NO), and indole-3-acetic acid (IAA). The major metabolites are DMT-NO, and IAA. In the rabbit liver, all five compounds were found, however, in the rabbit brain no 6-OH metabolites were identified. Since a small fraction of exogenous DMT is excreted in urine unchanged despite taken with MAO inhibitors[1], it is possible that oxidative deamination of DMT by MAO is not the exclusive metabolic pathway in humans.

The subjective effects of intravenous administration of DMT (typical dose 0.1 – 0.4 mg/kg;) reach to maximum at about 5 min and disappear by 30 min. Intramuscular effects of DMT hydrochloride or DMT fumarate (reported dose 0.2- 1 mg/kg;) have a quick incipience within 2 – 5 min and can last 30 - 60 min, the effects are generally weaker than intravenous or inhalation route. Per os, the hallucinogenic effects of DMT in the formulation of ayahuasca, which contains MAO inhibitors (0.6 - 0.85 mg/kg DMT), generally have an onset within 60 min, peak at 90 min and can remain for approximately 4h. The typical doses of smoked or inhaled free-base DMT are 40 - 50 mg, although dose may be as high as 100mg. The effect of these doses of smoked DMT is rapid, similar to that of intravenous administration, but lasts less than 30 min. Intranasal free-base DMT was inactive (0.07 – 0.28 mg/kg), as was DMT administered rectally (1.7 mg/kg) of the bioxalate salt[1].

- *Pharmacodynamics*

DMT orally ingested via ayahuasca produces neurochemical and behavioral effects, such as sympathomimetic effects, decreases in motor activity, impairment of cognitive function, raise of prolactin and cortisol levels, and reduction of lymphocytes[1].

In humans, chronic use of ayahuasca may change brain structure, correlating with increased thinning of the posterior cingulate cortex, though not showing increased psychopathology or worse neuropsychological performance in the users[10].

Although little or no tolerance develops to the subjective effects, several early studies demonstrated that tolerance can be developed peripheral effects, namely cardiovascular, with DMT administration[1].

Molecular Targets

The action mechanisms for psychedelics are currently not all clear, but most studies focus on DMT as a partial agonist of serotonin (5-HT) receptors. 5-HT2A receptor is pointed to be the main target of classic serotonergic-mediated psychedelic compounds, but also not sufficient for hallucinogenic effects and 5-HT2C and 5-HT1A receptors may play important roles as well[11]. Two other receptors have been investigated as possible targets for DMT, the trace amine receptor (TAAR) family and sigma-1 receptors (S1R). Here we will provide a description of the studies conducted with these receptors.

- *5-HT2*

The known subjective effects of DMT have been attributed essentially to the 5-HT receptors[12], already widely used with affinity for other psychedelic receptors, the best described are 1A, 2A, and 2C receptor subtypes, with focus at 5-HT2A receptors. DMT binds all 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5A, 5-HT6 and 5-HT7 receptors with affinities (Ki) between 39 nM to 2.1 μM[13]. The inhibition coefficient (Ki) of DMT at the human 5-HT2A receptor is reported as 130 nM[13]. DMT acts as agonist at the 5-HT1A and 5HT2C receptors as well.

Like other classic psychedelics, DMT increases 5-HT levels and/or decrease its turnover. Moreover, doses of ayahuasca 15 or 30-fold higher than usually used ritual doses increased serotonergic neurotransmission. Although DMT inhibited 5-HT transport with a Ki of 4 μM at the serotonin reuptake transporter (SERT), there are no conclusions about the mechanism of interaction. As happens with amphetamine derivatives such as para-chloroamphetamine (pCA) and MDMA, SERT can be induced to operate in the reverse direction by SERT substrates, including 5-HT and tyramine. Blough et al. (2014)[14] found that DMT was a SERT ligand, with an EC50 value of 114 nM. The most probable mechanism is DMT-induced release of neuronal 5-HT, in a way similar to that of amphetamines such as MDMA[15].

- *Sigma-1*

The sigma receptor was originally proposed as a subtype of opioid receptors, but later studies confirmed them as non-opioid receptors playing a more diverse role in intracellular signaling, apoptosis and metabolic regulation[16].

Sigma-1 receptors are intracellular receptors acting as chaperone proteins that modulate Ca2+ signaling through the IP3 receptor. S1Rs and ion channels may play an important role in neuroplasticity processes, resulting in the need for lower doses to reach therapeutic concentrations. Of particular interest is the non-linear dose response curve of S1R agonists in *in vitro* experiments, in which S1R agonists are active,

e.g. learning and memory processes, depression and anxiety. The S1R, at the mitochondrial-associated endoplasmic reticulum membrane, is responsible for mitochondrial metabolic regulation and promotes mitochondrial energy depletion and apoptosis. Studies have demonstrated that they play a role as a modulator of ion channels and regulate lipid transport and metabolism, neuritogenesis, cellular differentiation and myelination in the brain. S1R polymorphism is associated with an increased risk of schizophrenia and differential activation of the prefrontal cortex and the severity of Alzheimer's. S1R antagonists show antipsychotic effects in vivo[15,16].

Given that steroids bind to sigma receptors, it is possible that it serves as a link among endocrine, nervous, lung, kidney, heart, intestines, liver, sexual and immune systems; S1R are more dense in the dentate gyrus of the hippocampus, facial nucleus, thalamic and hypothalamic nuclei, with moderate densities found in the striatum, cerebellum, dorsal raphe nucleus and locus coeruleus[16].

A report now demonstrates that DMT targets and binds to the S1R with a moderate affinity (K_D of 14.75 μM)[17]. Though, the K_D of DMT at the S1R is approximately 30-fold superior than the highest concentrations achieved by intravenous administration, therefore making it very unlikely that endogenous DMT could be binding and having a physiological role with these receptors[15].

- *Trace amine-associated receptor*

Tryptamine is a trace-amine, primary amines that are natural side products of synthesis or metabolism of monoamine precursors. Trace amines are found at soft levels within the mammalian/vertebrate brain at concentrations approximately 100 times lower than traditional monoamines[18].

TAAR are a family of vertebrate, rhodopsin-like, type A, G protein-coupled receptors. Although 26 sub- types of TAAR have been identified in mammalian species, they all belong to nine sub-families (TAAR1-9). Humans express a single functional variant of 6 of the TAAR family members (TAAR1, 2, 5, 6, 8 and 9), with TAAR3, 4 and 7 subtypes appearing to be pseudogenes. One of the key challenges in the TAAR field is the mostly low receptor expression levels, at least under basal conditions, which necessitates the use of the most stringent of reagents and methodologies in order to prevent cross-reactivity[1].

In the rat, highest expression levels of TAAR1 were perceived in the olfactory bulb, nucleus accumbens/olfactory tubercle, prefrontal cortex and other cortical regions, midbrain regions consisting of substantia nigra and ventral tegmentum, cerebellum, and pons/medulla. Outside of the central nervous system, TAAR1 is essentially expressed in pancreatic β-cells, stomach and intestines in human, rat and mouse. Recent studies with specific anti-human TAAR1 antibodies, revealed a similar peripheral distribution of TAAR1 in human tissues as previously described in mice, with restricted expression in pancreatic islets, duodenum and jejunum and pylorus of the stomach[19]. In addition, several groups have reported TAAR1 expression in both human and mouse leukocytes and in human breast cancer tissue. However, the commercial anti-TAAR1 antibody used in these studies is not entirely reliable [20]. Recent research has reported seven rare protein disturbing variants in TAAR1 that could elevate the risk for schizophrenia. TAAR1 has also been shown to interact with two other strong candidate genes, namely the dopamine transporter (DAT) and DRD2 from the dopaminergic pathway[21].

The binding potency of DMT to TAAR1 compared to its precursor tryptamine, is higher in both rat (0.13 μM to 2.2 μM) and mouse (1.4 μM to 3.3 μM). In humans, the E50 value, which indicates how much of a drug is needed to achieve 50% of the maximum response, was lower in comparison to tryptamine [20,22], suggesting better affinity due to methylation.

The role of TAAR receptors is not deciphered yet. TAAR1 appears to function as an endogenous rheostat, maintaining central neurotransmission within defined physiological limits, in part through receptor heterodimerization yielding biased signaling outputs. TAAR1 knock-out mice have been reported to manifest schizophrenia-like behaviors, apparently related with the dopaminergic system[23]. In addition, pre-clinical animal models have identified TAAR1 as a novel target for drug addiction and metabolic disorders[19]. Growing evidence also suggests a role for TAARs in regulating immune function and in the central nervous system, where it is believed to modulate monoaminergic neurotransmission, thus affecting a number of neural networks and processes[24,22].

State of art about DMT endogenous role

The greatest methodological setback to research in DMT and to its possible binding to the above-cited receptors is the infimum amount of DMT produced endogenously. Therefore, two theories have arisen that try to explain how the concentration of DMT could locally rise. On one hand, it has been suggested that DMT could reach high local concentrations in neuron endings through a process involving uptake across the plasma membrane, a mechanism identical to those described for known neurotransmitters. The affinity of DMT for SERT and vesicular monoamine transporter (vMAT) was investigated and inconsistent results point to the existence of affinity, EC50 value of 114 nM to SERT, and vMAT was tested with methodological frailties as well. Still, having some affinity for SERT and vMAT is not a leaden argument, as there are more compounds that are substrates for the SERT and vMAT for which there is no evidence that they are accumulated in vesicles. As Nichols (2017) suggests[15], an important experiment that would resolve this conflict could be incubating radioactively-labeled DMT with synaptosomes from rats that had been treated with a MAO inhibitor. On the other, DMT accumulation in the CNS would be due to the active transport of DMT through the blood-brain barrier, but the existing studies reveal important methodological problems and non-extrapolated conclusions on brain/plasma ratio of the molecule, which is not a specific proof of active transport into the brain[15].

Strassman has suggested that the pineal gland excretes huge quantities of DMT during extremely stressful life events, notably birth and death. For this to happen, the pineal gland would need to produce very promptly (over seconds) about 25 mg of DMT. The mean daily production of melatonin from the pineal gland is approximately 30 μg, about 1/1000 of the weight of DMT needed to get an effect he describes as breakthrough into the “DMT space” [11].

The lack of recent research with more precise methodology has made difficult the elucidation of its importance and mechanisms. However, while endogenously the work has not yet reached great achievements, research with exogenous DMT has advanced steadily. The interaction of the molecule with the above-described receptors may underlie important advances in psychiatric pharmacology. What is already known about the therapeutic potential of DMT is described next.

Therapeutic Potential of N,N-dimethyltryptamine

The therapeutic potential of DMT has been studied mainly in anxiety, depression and substance abuse disorders. Here we review the evidence for each of these pathologies.

Anxiety

A case control study with a sample of Santo Daime (religious organization) members reported reductions in associated symptomatology of anxiety and depression after a first consumption of Ayahuasca[25]. However, this has been contradicted[26]. Moreover, these studies were carried out under a religious context, which may constitute a biasing factor.

Studies using rodent models, by ruling out the ceremonial religious aspects, can contribute to elucidate the role of the brew *per se* into the neurobiological mechanisms of ayahuasca on anxiety-related behavior. A recent essay in zebrafish suggests that small amounts (0.1, 0.5 mL/L) of ayahuasca do not affect locomotion and reduce anxiety-like behavior in zebrafish, while increased doses of the drug lead to crescent anxiogenic effects[27].

Depression

More recently, two open-label trials conducted by the same group [28,29] evaluated the effects of a unique dose of ayahuasca in psychiatric depressive inpatients. In the former, a statistically significant reduction of up to 82% was observed in depressive scores in three scales between baseline and 1, 7, and 21 days after the administration. Furthermore, ayahuasca administration did not produce episodes of mania or hypomania, neither did it lead to increases in the thinking disorder subscale. In the latter, the authors reported significant decreases in scores on the same depression scales from 80 minutes after administration to day 21. Nevertheless, they reported increases in dissociative symptoms. Sanches et al. (2016)[29] also included a SPECT assessment which describes increased blood perfusion in the left nucleus accumbens, left subgenual area and right insula, these are brain regions related to the regulation of mood and emotional states.

A case control study in 2015 found differences in cortical thickness in regular users of psychedelics. Ayahuasca users showed significant cortical thickness differences in midline structures of the brain, with thinning in the posterior cingulate cortex, a key node of the default mode network (DMN)[10]. A case study from the same year demonstrated that ayahuasca intake leads to a decrease in the activity of core DMN structures as well[30].

Later in 2017 an open-label uncontrolled study in 16 healthy volunteers, ayahuasca consumption induced post-acute neurometabolic and connectivity modifications using magnetic resonance spectroscopy. The results support the involvement of glutamate neurotransmission in the effects of psychedelics in humans. They further rely neurometabolic changes in the posterior cingulate cortex and increased connectivity between the anterior cingulate cortex and medial temporal lobe structures involved in emotion and memory[31].

These findings are interesting because the resting state brain networks, DMN in particular, have been reported to be altered in several psychopathological conditions such as depression and anxiety. 5HT2A

agonists can potentially induce structural changes in brain tissue by stimulating neurotrophic and transcription factors associated with synaptic plasticity. The functional connectivity of the anterior portions of DMN, involved in self-referential and emotional processes, was positively correlated with anxiety and depression scores, whereas posterior areas of the DMN, involved in episodic memory and perceptual processing were negatively correlated with anxiety and depression scores. The dissociation between anterior and posterior cortical midline regions, raises the possibility of a functional specialization within the DMN in terms of self-referential tasks and contributes to the understanding of the cognitive and affective changes in depressive and anxiety states [32].

Substance Dependence

Observational studies reported remission of alcohol, changes in behavior and perspectives after intake of ayahuasca[33-35]. Fábregas et al. (2010)[36] adds that the effects were preserved at one-year follow-up. In another case series study, the authors found statistically significant decreases in cocaine use after an ayahuasca assisted therapy in a sample with no prior experience with it. Some other descriptive studies, such as observational pilot studies and reports of informal interviews, have presented preliminary knowledge suggesting a potential beneficial role for ayahuasca in the treatment of substance use disorders [37].

An investigation with mice was carried out through the development of ethanol-induced behavioral sensitization and on a post-sensitization. It revealed that ayahuasca not only inhibits initial behaviors associated with the beginning and progress of ethanol addiction, but also showed effectiveness in annulling chronic drug effects expression, inhibiting the return of ethanol-induced behavioral sensitization when administered in the ethanol-associated environment [38].

Conclusion

Psychedelics are intriguing drugs that induce transient but intense modifications in perception, emotion and cognitive processes. While endogenous DMT does not seem to induce remarkable modifications, research into DMT as a therapeutic option has proven to be a candidate for the future. The incidence of psychotic episodes during ayahuasca ingestion appears to be rare and can be controlled by common antipsychotics as quetiapine [39,40]. Results indicated that structured ayahuasca consumption was medically safe and exhibited a potential protective psychological effect. Most of the psychedelics like psilocybin act almost exclusively on the serotonergic system, while DMT has affinities to sigma-1, monoaminergic, and trace amine-associated receptors which have some evidence linked with psychiatric diseases [30]. An increasing number of papers suggest promising benefits in mood and psychiatric symptoms in the areas of substance use disorders, anxiety and depression. DMT is the main compound of ayahuasca and its psychedelic effects have been reported as relevant in these clinical areas. However, other known compounds of the blend such as harmine and harmaline also revealed anxiolytic effects[41]. More clinical research with the use of pure DMT has to be done to disambiguate the contributions of each substance. The most recent studies report a fast and sustained improvement in patients with these diseases, thereby possibly opening way for new drugs in the treatment of such common pathologies[42], where a lack of solutions[43] is notable.

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References

1. Carbonaro, T. M. & Gatch, M. B. Neuropharmacology of N,N-Dimethyltryptamine. *Brain Research Bulletin* 1–61 (2016). doi:10.1016/j.brainresbull.2016.04.016
2. Barker, S. A., McIlhenny, E. H. & Strassman, R. A critical review of reports of endogenous psychedelic N, N-dimethyltryptamines in humans: 1955-2010. *Drug Test. Analysis* **4,** 617–635 (2012).
3. Barker, S. A., Borjigin, J., Lomnicka, I. & Strassman, R. LC/MS/MS analysis of the endogenous dimethyltryptamine hallucinogens, their precursors, and major metabolites in rat pineal gland microdialysate. *Biomed. Chromatogr.* **27,** 1690–1700 (2013).
4. Heekeren, K. *et al.* Prepulse inhibition of the startle reflex and its attentional modulation in the human S-ketamine and N,N-dimethyltryptamine (DMT) models of psychosis. *J Psychopharmacol* **21,** 312–320 (2016).
5. Daumann, J. *et al.* Neuronal correlates of visual and auditory alertness in the DMT and ketamine model of psychosis. *J Psychopharmacol* **24,** 1515–1524 (2009).
6. Tupper, K. W. The globalization of ayahuasca: harm reduction or benefit maximization? *Int. J. Drug Policy* **19,** 297–303 (2008).
7. Carhart-Harris, R. L. *et al.* Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* **3,** 619–627 (2016).
8. Garcia-Romeu, A., Kersgaard, B. & Addy, P. H. Clinical applications of hallucinogens: A review. *Experimental and Clinical Psychopharmacology* **24,** 229–268 (2016).
9. Rabbit Lung Indolethylamine N-Methyltransferase. 1–10 (1998).
10. Bouso, J. C. *et al.* Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. *European Neuropsychopharmacology* **25,** 483–492 (2015).
11. Nichols, D. E. Hallucinogens. *Pharmacology and Therapeutics* **101,** 131–181 (2004).
12. Halberstadt, A. L., Koedood, L., Powell, S. B. & Geyer, M. A. Differential contributions of serotonin receptors to the behavioral effects of indoleamine hallucinogens in mice. *J Psychopharmacol* **25,** 1548–1561 (2010).
13. Keiser, M. J. *et al.* Predicting new molecular targets for known drugs. *Nature* **462,** 175–181 (2009).
14. Blough, B. E. *et al.* Interaction of psychoactive tryptamines with biogenic amine transporters and serotonin receptor subtypes. *Psychopharmacology* **231,** 4135–4144 (2014).
15. Nichols, D. E. N,N-dimethyltryptamine and the pineal gland: Separating fact from myth. *J Psychopharmacol* 1–7 (2017).
16. Rousseaux, C. G. & Greene, S. F. Sigma receptors [σRs]: biology in normal and diseased states. *Journal of Receptors and Signal Transduction* **197,** 1–62 (2016).
17. Fontanilla, D. *et al.* The Hallucinogen N,N-Dimethyltryptamine (DMT) Is an Endogenous Sigma-1 Receptor Regulator. *Science* **323,** 934–937 (2009).

18. Zucchi, R., Chiellini, G., Scanlan, T. S. & Grandy, D. K. Trace amine-associated receptors and their ligands. *British Journal of Pharmacology* **149,** 967–978 (2009).
19. Raab, S. *et al.* Incretin-like effects of small molecule trace amine-associated receptor 1 agonists. *Molecular Metabolism* **5,** 47–56 (2016).
20. Bunzow, J. R. *et al.* Amphetamine, 3,4-Methylenedioxymethamphetamine, Lysergic Acid Diethylamide, and Metabolites of the Catecholamine Neurotransmitters Are Agonists of a Rat Trace Amine Receptor. *Molecular Pharmacology* 1–8 (2001).
21. John, J. *et al.* Possible role of rare variants in Trace amine associated receptor 1 in schizophrenia. *Schizophrenia Research* 1–6 (2017). doi:10.1016/j.schres.2017.02.020
22. Berry, M. D., Gainetdinov, R. R., Hoener, M. C. & Shahid, M. Pharmacology of human trace amine-associated receptors: Therapeutic opportunities and challenges. *Pharmacology and Therapeutics* **180,** 161–180 (2017).
23. Shi, X. *et al.* Genetic Polymorphisms Affect Mouse and Human Trace Amine-Associated Receptor 1 Function. *PLoS ONE* **11,** e0152581–14 (2016).
24. Szabo, A. Psychedelics and Immunomodulation: Novel Approaches and Therapeutic Opportunities. *Front. Immunol.* **6,** 1–11 (2015).
25. Barbosa, P. C. R., Giglio, J. S. & Dalgalarrondo, P. Altered States of Consciousness and Short-Term Psychological After-Effects Induced by the First Time Ritual Use of Ayahuasca in an Urban Context in Brazil. *Journal of Psychoactive Drugs* **37,** 193–201 (2005).
26. Santos, R. G., Landeira-Fernandez, J., Strassman, R. J., Motta, V. & Cruz, A. P. M. Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. *Journal of Ethnopharmacology* **112,** 507–513 (2007).
27. Savoldi, R. *et al.* Behavioral Changes Over Time Following Ayahuasca Exposure in Zebrafish. *Front. Behav. Neurosci.* **11,** 37–9 (2017).
28. Osório, F. de L. *et al.* Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Rev. Bras. Psiquiatr.* **37,** 13–20 (2015).
29. Sanches, R. F. *et al.* Antidepressant Effects of a Single Dose of Ayahuasca in Patients With Recurrent Depression. *Journal of Clinical Psychopharmacology* **36,** 77–81 (2016).
30. Palhano-Fontes, F. *et al.* The Psychedelic State Induced by Ayahuasca Modulates the Activity and Connectivity of the Default Mode Network. *PLoS ONE* **10,** e0118143–13 (2015).
31. Sampedro, F. *et al.* Assessing the Psychedelic 'After-Glow' in Ayahuasca Users: Post-Acute Neurometabolic and Functional Connectivity Changes Are Associated with Enhanced Mindfulness Capacities. *Int. J. Neuropsychopharm.* **20,** 698–711 (2017).
32. Coutinho, J. F. *et al.* Default mode network dissociation in depressive and anxiety states. *Brain Imaging and Behavior* **10,** 147–157 (2015).
33. Grob, C. S. *et al.* Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. *J. Nerv. Ment. Dis.* **184,** 86–94 (1996).
34. Kuc, D. Evidence of health and safety in American members of a religion who use a hallucinogenic sacrament. 1–9 (2008).
35. bregas, J. M. F. *et al.* Assessment of addiction severity among ritual users of ayahuasca. *Drug and Alcohol Dependence* **111,** 257–261 (2010).
36. Thomas, G., Lucas, P., Capler, N. R., Tupper, K. W. & Martin, G. Ayahuasca-assisted therapy for addiction: results from a preliminary observational study in Canada. *Curr Drug Abuse Rev* **6,** 30–42 (2013).
37. Domínguez-Clavé, E. *et al.* Ayahuasca: pharmacology, neuroscience and therapeutic potential. *Brain Research Bulletin* 1–56 (2016). doi:10.1016/j.brainresbull.2016.03.002
38. Oliveira-Lima, A. J. *et al.* Effects of ayahuasca on the development of ethanol-induced behavioral sensitization and on a post-sensitization treatment in mice. *Physiology & Behavior* **142,** 28–36 (2015).
39. Santos, dos, R. G., Bouso, J. C. & Hallak, J. E. C. Ayahuasca, dimethyltryptamine, and psychosis: a systematic review of human studies. *Therapeutic Advances in* **7,** 141–157 (2017).
40. Paterson, N. E., Darby, W. C. & Sandhu, P. S. N,N-Dimethyltryptamine–Induced Psychosis. *Clinical Neuropharmacology* **38,** 141–143 (2015).

41. Santos, dos, R. G., Osório, F. L., Crippa, J. A. S. & Hallak, J. E. C. Antidepressive and anxiolytic effects of ayahuasca: a systematic literature review of animal and human studies. *Rev. Bras. Psiquiatr.* **38,** 65–72 (2016).
42. Kessler, R. C. & Bromet, E. J. The Epidemiology of Depression Across Cultures. *Annu. Rev. Public Health* **34,** 119–138 (2013).
43. Benefits: A Meta-Analysis of Data Submitted Initial Severity and Antidepressant to the Food and Drug Administration. 1–9 (2008). doi:10.1371/journal

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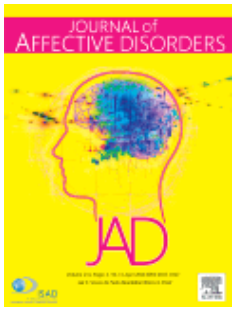

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